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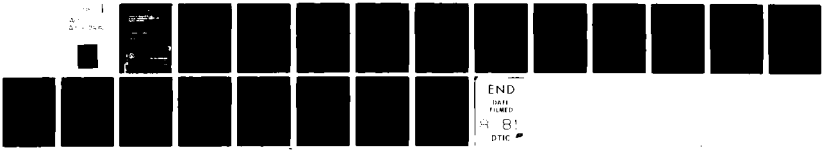

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EFFECTS OF TRIAZOLAM (0.5 mg) ON SLEEP, PERFORMANCE, MEMORY, AND AROUSAL THRESHOLD

C. L. SPINWEBER & L. C. JOHNSON

REPORT NO. 81-1

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EFFECTS OF TRIAZOLAM (0.5 mg) ON SLEEP, PERFORMANCE, MEMORY, AND AROUSAL THRESHOLD

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SUMMARY

Currently marketed sleeping pills are long-acting drugs which impair morning performance following bedtime administration, thus rendering them unsuitable for use in operational settings. Triazolam, a newer, short-acting benzodiazepine, was evaluated to determine its usefulness as a hypnotic and to measure its effects on performance, memory, and arousal threshold. The rapid metabolism and clearance of triazolam suggested that it might promote improved sleep without producing a drug-induced performance impairment the following morning.

Twenty male poor sleepers, mean age 21 ± 2.37 years, were studied. To qualify as a poor sleeper, subjects had to rate their sleep quality as "poor" or "very poor," report a usual sleep latency greater than 45 minutes, and indicate that the problem had persisted for at least 6 months. To meet EEG sleep criteria on the screening night, poor sleepers had to exhibit sleep latencies of 30 minutes or longer and have at least 5% of their total sleep time in Stages 3 + 4, slow wave sleep.

Following the screening night, subjects received placebos in a single-blind paradigm for 3 consecutive baseline nights. Following the placebo-baseline nights, 10 subjects received 0.5 mg triazolam for 6 nights while the other 10 continued to receive placebo in a double-blind paradigm. After the 6 treatment nights, all subjects received placebo on 2 withdrawal nights. All-night sleep EEGs were recorded according to the usual laboratory procedures.

Performance batteries were administered 20–40 minutes after the morning awakening. Tests included the Wilkinson 4-Choice Reaction Time Test, the Digit Symbol Substitution Test, the Williams Word Memory Test, and the Card Sorting Task. On night 10, the performance night, subjects were aroused from Stage 2 sleep, at 1.5, 3, and 5 hours post-drug ingestion, to perform the same tasks, in order to assess the acute effects of triazolam on performance. In the morning following night 10, subjects were presented with the Memory Checklist. This list contained the 90 words which were presented in the Williams Word Memory Task during nighttime test sessions plus 90 filler words. Subjects were instructed to pick out the words they remembered from the nighttime sessions.

Arousal threshold was obtained on 3 study nights. Tones were played over a loudspeaker and incremented in 5 dB steps until the sleeper was awakened by the tone.

Triazolam was found to be an effective hypnotic which significantly reduced sleep latency and increased total sleep time. Morning performance was unimpaired by bedtime administration of triazolam. However, at 1.5, 3, and 5 hours post-administration, ability to perform was significantly lowered. In addition, triazolam was found to produce anterograde amnesic effects--impairment of memory for stimuli presented during the acute phase of drug action. Triazolam also significantly elevated arousal threshold during the night.

Triazolam is suitable for use as a sleeping pill in settings in which personnel will be scheduled for 7.5 hours of sleep. However, since triazolam does impair ability to perform visuo-motor and cognitive tasks for up to 5 hours post-administration, impairs memory for events occurring during the night, and elevates arousal threshold, its usefulness in operational settings in which there might be a need to arouse personnel to perform duties is limited.

INTRODUCTION

In sleep laboratory studies, triazolam (Halcion), a triazolobenzodiazepine, has been demonstrated to be an effective hypnotic in doses ranging from 0.25–1.0 mg.[1-9] In addition, results of outpatient studies and other investigations which used self-report measures to evaluate hypnotic efficacy have shown that sleep is subjectively improved after triazolam administration.[10-18]

Pharmacokinetic measures indicate that both triazolam and its active metabolite, 7-α-hydroxy triazolam, have short half-lives, reported to be within the range of 2.1–10 hours.[19-21] The relatively rapid metabolism and clearance of triazolam suggest that, at least at lower doses within the effective range, this benzodiazepine may promote improved sleep without producing a drug-induced performance impairment the following morning. Several studies have assessed morning performance following bedtime triazolam administration.[2,5,7,10,17,22] The results of these studies differ, depending upon dose size, time post-ingestion when tests were administered, and the type of tasks used. Only one of these performance studies used insomniacs as subjects.[5]

Acute effects of triazolam (0.25 mg and 0.5 mg) on performance have been demonstrated at 3.5 hours post-administration in testing following arousal from sleep.[2] Nicholson and Stone[7] have reported an impairment of visuo-motor performance up to 5 hours post-administration of a 0.25 mg dose during daytime testing in subjects who remained awake. We believe that ours is the first study of benzodiazepine hypnotics to employ multiple systematic arousals from sleep, designed to delineate temporal parameters of acute effects and provide behavioral correlates of benzodiazepine pharmacodynamics in the sleeping subject.

MATERIALS AND METHODS

Subjects

Twenty male poor sleepers, mean age 21 ± 2.37 years, were studied. Poor sleep was defined by both EEG and subjective criteria. Subjective criteria included responses to a questionnaire designed to elicit the individual's reports of his sleep quality. To qualify as a poor sleeper, subjects had to rate their sleep quality as "poor" or "very poor," indicate a usual sleep latency greater than 45 minutes (sleep onset insomnia), and report having this sleep onset problem for at least 6 months. The subject's subjective report was discussed further in a personal interview. To meet EEG sleep criteria on the screening night, poor sleepers had to exhibit sleep latencies (time from lights out to the onset of Stage 2 sleep) of 30 minutes or longer and have at least 5% of their total sleep time in slow wave sleep (SWS) (Stages 3 + 4). During screening nights, average sleep latency for the 20 subjects was 53.6 ± 34 minutes.

Subjects were screened for possible psychiatric conditions, sensitivity to benzodiazepines, alcohol or drug abuse, and recent illnesses. All subjects were in good health and denied current or recent use of any type of sleep medication or other drugs. There were no sleep complaints other than those associated with falling asleep.

All subjects were informed about the general nature of the experiment and willingly signed Informed Consent and Privacy Act statements. All subjects were asked to refrain from napping and taking drugs or alcohol during the course of the study. Breath analyzer and urine tests, used aperiodically, indicated no detectable use of alcohol or other drugs during the study.

Based on screening night findings, 20 possible poor sleepers were rejected because of sleep latencies less than 30 minutes. Two subjects were dropped from the study during placebo-baseline due to concern over poor academic performance. No subjects were dropped because of side effects.

Procedure

A parallel, three-phase design was employed. Subjects who qualified as poor sleepers on the screening night went on to complete 11 additional nights of the 12-night protocol (see Table 1).

Following the screening night, subjects received placebos in a single-blind paradigm for 3 consecutive baseline nights. Following the placebo-baseline nights, 10 subjects received 0.5 mg triazolam for 6 nights while the other 10 continued to receive placebo in a double-blind paradigm. After the 6 treatment nights, all subjects received placebo on 2 withdrawal nights. The placebo or drug tablet was given at 2145 hours each night. Lights out was at 2200 and subjects were awakened at 0530.

Each subject slept in an electrically shielded, air-conditioned room with soundproofing. All electrophysiological variables were recorded on an 8-channel Beckman dynograph. The electro-oculogram (EOG) was recorded from biopotential electrodes placed on the outer canthus of each eye. The EEGs were obtained by use of silver chlorided disc electrodes from C_3 and O_1 electrode placements referenced to linked mastoids ($A_1 + A_2$). Both EOG and EEG time constants were 0.3 seconds. Sleep stages were determined according to standard criteria.[23]

TABLE 1

Triazolam Study Protocol

	Condition											
		Placebo—Baseline			Treatment (Placebo or Triazolam)						Placebo—Withdrawal	
Night #	1	2	3	4	5	6	7	8	9	10	11	12
Procedure	(S)	(E)*	A	(C)*	(E)*	A	(E)*	A	(C)*	(P)	(E)*	(E)*

Procedure Code

S = Screening Night
E = All-night EEG
A = Arousal Night
C = AEP Night
P = Performance Night

(◯) Morning Testing

* Paired-Associates Testing

Subjects were familiarized with all questionnaires and trained on all tasks in a practice session conducted prior to night 1 of the study.

Bedtime and Morning Questionnaires. The subjects completed a Bedtime Questionnaire each evening which required the subject to report side effects, unusual events occurring that day, naps, alcohol consumption, and his readiness for bed. The Stanford Sleepiness Scale (SSS)[24] was also included in this questionnaire. Upon awakening at 0530, the subjects completed a Morning Questionnaire which included the SSS, and also required the subject to estimate sleep latency, total sleep time, and number of awakenings, to list any physical complaints, and to rate the effectiveness of the pill and evaluate sleep quality.

Sleep Measures. Sleep latency (time from lights out to the onset of Stage 2) was scored for all study nights. Mean sleep latencies were derived for each subject for each condition: placebo-baseline (nights 2–4), treatment (nights 5–10), and placebo-withdrawal (nights 11–12).

Sleep stage data were obtained for comparison on nights of uninterrupted sleep (*i.e.*, on study nights on which subjects were not awakened to perform tasks or respond to tones or on nights when auditory evoked potentials (AEPs) were obtained). For the three conditions, sleep measures were obtained as follows: placebo-baseline (night 2), treatment (mean of nights 5 and 7), and placebo-withdrawal (mean of nights 11 and 12). Sleep measures were: Total Sleep in minutes (the sum of minutes in Stages 2, 3, 4, and REM); Stage 1 percent (minutes of Stage 1 divided by the total bed time x 100); Stage 2 percent, Stage 3 percent, Stage 4 percent, and Stage REM percent (minutes in each stage divided by Total Sleep x 100); Sleep Efficiency (Total Sleep divided by Total Bedtime x 100); Wake Time (minutes awake while in bed); Wake percent (minutes awake divided by Total Bedtime x 100).

Morning Performance and Mood Testing. Performance and mood test batteries were administered approximately 20–40 minutes after the morning awakening following nights 1, 2, 4, 5, 7, 9, 10, 11, and 12. Data from testing following the screening night (night 1) were not included in the data analysis. Morning batteries included two subjective mood scales, the NHRC Mood Scale and the Profile of Mood States (POMS), and several performance tests, including the Wilkinson 4-Choice Reaction Time Test (performed for 11 minutes) and the Digit Symbol Substitution Test. These tests have been described in detail in a previous publication.[25] The test battery also included the Williams Word Memory Test[26]: this task is a test of short-term memory. Subjects heard a tape-recorded list of 15 words. The voice on the tape said each word, spelled the word, and then repeated each word again. During list presentation, the subject wrote down each word. At the end of the 15-word presentation, the subject was allowed 3 minutes to write down as many of the words as he could recall. Two lists of words were presented during each performance battery. The subjects also performed the Card Sorting Task: this timed task required subjects to sort a deck of 36 numbered playing cards (cards numbered 2–10 in each of 4 suites) first into 4 piles according to suite and then into 9 piles according to number. Time (in seconds) to complete the sorting task was recorded.

The effects of triazolam on retention of material learned prior to drug administration were evaluated through use of a paired associate (P-A) learning task, a modified version of Ekstrand's memory test.[27] On study nights 2, 4, 5, 7, 9, 11, and 12, approximately 1 hour prior to drug

administration, the subject learned 10 word pairs from a tape-recorded list. The first word of each pair was a 3-letter noun selected from the 10–40 frequency range[28] and the second was an unrelated adjective selected from the 10–20 frequency range. The tape first presented the 10 word-pairs, then presented the first word of each pair in a random order to permit the subject to give the response. If the subject was unable to give all response words correctly, a list of the 10 pairs was presented again. Presentation of the 10 pairs followed by the testing procedure continued until the subject had learned all 10 pairs. Morning recall of the 10 pairs was tested in two ways: in P-A Recall, the subject was required to write down the response word when presented with a list of the 10 nouns. In P-A Matching, the subject was required to match nouns and adjectives of the pairs. For both tasks, number correct was recorded.

Performance and Mood after Arousal from Sleep. On night 10, the performance night, subjects were aroused from Stage 2 sleep during three preestablished time windows--90–100 minutes, 180–200 minutes, and 270–300 minutes after lights out--to complete performance and mood tests. Performance and mood testing during these time windows generally occurred at times 1.5, 3, and 5 hours post-drug ingestion. These nighttime batteries differed from the morning batteries in two aspects only: the SSS was administered in place of the POMS and the 4-Choice Reaction Time Test was performed for 6 rather than 11 minutes.

Following completion of each test battery, the subjects were instructed to go back to sleep. Latency of the return to sleep was also recorded.

In the morning following night 10, subjects were presented with the Memory Checklist. This list contained the 90 words which were presented in the Williams Word Memory Task during nighttime test sessions plus 90 filler words. Subjects were instructed to pick out the words they remembered from the nighttime sessions.

Arousal Threshold Procedure. The threshold for arousal from sleep was obtained on 3 recording nights: night 3 (placebo-baseline), night 6 (second treatment night), and night 8 (fourth treatment night). Tones were delivered over a loudspeaker positioned approximately 46 cm above the sleeper's head. The subject's threshold for tones while awake was obtained prior to lights out. During arousals from sleep, tones were begun at 20 dB above the awake threshold and were incremented in 5 dB steps until the subject made the behavioral (three button pushes) and verbal ("I'm awake") responses. Tones were 2 seconds long and occurred at 16-second intervals. Arousals were scheduled to reveal the time course of action of triazolam and were performed six times: #1: during the first Stage 2 sleep, 5 minutes after the sleep onset; #2: during the first SWS (Stage 3 or Stage 4), 20 minutes after the return to sleep following the first arousal; #3: in Stage 2, 150–210 minutes after lights out (0030–0130); #4: in Stage 2, 270–330 minutes after lights out (0200–0330); #5: in Stage 2, 370–430 minutes after lights out (0410–0510); #6: the morning arousal, at 0530.

Additional criteria which had to be met to initiate arousal procedures were: (1) there could be no major (8 seconds or longer) body movement for 10 minutes prior to the arousal. (2) Stage 2 or SWS had to be well-defined for 5 minutes prior to the arousal. After the subject made the appropriate response, he was told to go back to sleep. The dB level for the highest tone presented and the latency (in minutes) from the time of the awakening to the return to sleep were recorded.

EEG Parameters. On-line EEG detection of spindles and delta was performed for nights 2, 4, 5, 7, 9, 11, and 12. AEPs were recorded on nights 4 and 9. These EEG findings are reported in detail elsewhere.[29]

Statistical Analysis. Mean placebo-baseline, mean treatment, and mean placebo-withdrawal scores were derived for each subject for the various measures. Mean data were statistically evaluated using between-groups t-tests on difference scores, derived by subtracting each subject's mean treatment or mean placebo-withdrawal score from his mean placebo-baseline score. For night 10 data, Analysis of Variance for Repeated Measures, with "Sessions" and "Groups" as factors, was used. Night-by-night data were also plotted, inspected, and appropriately tested if there was evidence of night-by-night effects. Additional analyses for specific measures are described in the results section. All tests were one-tailed unless otherwise stated.

RESULTS

Effects on Sleep. A night-by-night plot of mean sleep latencies is presented in Fig. 1. Mean sleep data by conditions are presented in Table 2. Triazolam significantly reduced sleep latency during treatment (t_{18} = 2.1051, $P < 0.025$). The medication also increased total sleep time (t_{18} = 2.3896, $P < 0.025$), sleep efficiency (t_{18} = 2.4279, $P < 0.025$), and decreased wake time (t_{18} = 2.32469, $P < 0.025$) and wake percent (t_{18} = 1.79634, $P < 0.05$) during treatment.

Stage 2 percent was increased (t_{18} = 4.3160, $P < 0.0005$) and Stage 4 percent was decreased (t_{18} = 2.1224, $P < 0.025$). Brain electrical activity was correspondingly altered: spindle rate per minute of NREM was elevated (t_{18} = 4.04, $P < 0.0005$) and delta rate per minute NREM sleep was reduced (t_{18} = 3.88, $P < 0.005$). (See Johnson and Spinweber[29] for a further discussion of spindle and delta count findings.) REM percent was reduced in the triazolam group during treatment (t_{19} = 3.0391, $P < 0.005$).

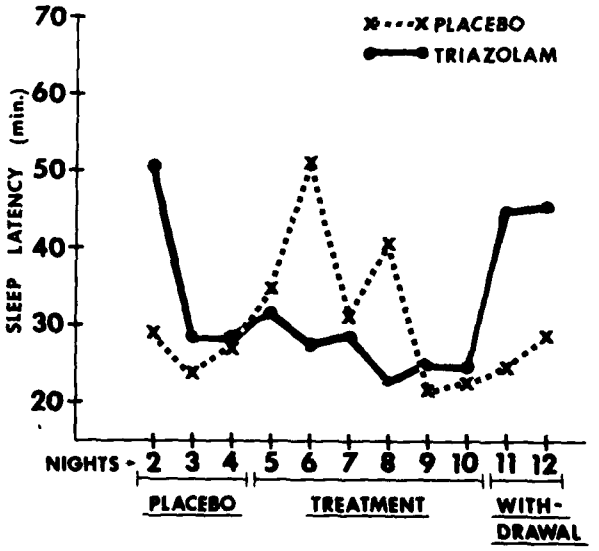

Fig. 1. Mean sleep latencies for nights 2–12.

TABLE 2

Mean Sleep Data by Conditions[a]

	Placebo Group		
	Placebo-Baseline $\bar{X}$ (± SD)	Treatment $\bar{X}$ (± SD)	Placebo-Withdrawal $\bar{X}$ (± SD)
Sleep latency (minutes)[c]	26.65 (7.56)	33.82 (17.95)	26.55 (9.09)
Spindles/minute NREM[e]	3.36 (1.31)	3.24 (1.57)	3.55 (1.41)
Delta/minute NREM[d]	40.92 (20.83)	39.65 (19.89)	39.66 (17.72)
Total sleep (minutes)[c]	389.65 (21.00)	392.07 (18.64)	398.87 (19.78)
Stage 1 percent	3.82 (1.54)	4.21 (1.56)	3.86 (2.02)
Stage 2 percent[e]	50.72 (9.03)	52.57 (8.98)	53.27 (6.40)
Stage 3 percent	8.03 (2.23)	7.59 (1.54)	7.42 (1.60)
Stage 4 percent[e]	11.00 (6.59)	9.36 (6.00)	9.72 (5.95)
REM percent[d]	30.25 (6.11)	30.48 (6.38)	29.58 (4.06)
Sleep efficiency[c]	87.04 (4.74)	87.60 (4.03)	89.20 (4.30)
Wake time (minutes)[c]	34.30 (19.23)	27.40 (16.27)	21.72 (9.70)
Wake percent[b]	7.66 (4.30)	6.13 (3.65)	4.86 (2.19)
	Triazolam Group		
	Placebo-Baseline $\bar{X}$ (± SD)	Treatment $\bar{X}$ (± SD)	Placebo-Withdrawal $\bar{X}$ (± SD)
Sleep latency (minutes)[c]	35.54 (23.96)	26.67 (7.34)	44.88 (35.30)
Spindles/minute NREM[e]	3.97 (2.23)	5.69 (2.69)	3.86 (1.95)
Delta/minute NREM[d]	47.52 (25.90)	32.08 (23.89)	37.66 (27.39)
Total sleep (minutes)[c]	373.95 (32.53)	406.45 (6.81)	381.12 (29.95)
Stage 1 percent	3.57 (1.61)	2.94 (1.57)	3.78 (1.30)
Stage 2 percent[e]	48.70 (7.45)	60.67 (5.26)	50.12 (7.66)
Stage 3 percent	10.95 (3.91)	9.03 (4.33)	9.30 (3.28)
Stage 4 percent[e]	9.45 (7.23)	4.89 (7.00)	8.09 (6.75)
REM percent[d]	30.89 (4.57)	25.40 (3.09)	32.48 (6.03)
Sleep efficiency[c]	83.43 (7.10)	90.77 (1.50)	85.04 (6.59)
Wake time (minutes)[c]	50.30 (35.87)	21.95 (8.35)	41.15 (34.53)
Wake percent[b]	11.24 (8.05)	4.90 (1.86)	9.19 (7.72)

[a] For sleep latency, means for conditions were computed as follows: Placebo-Baseline = Nights 2–4; Treatment = Nights 5–10; Placebo-Withdrawal = Nights 11–12; For other measures: Placebo-Baseline = Night 2; Treatment = Nights 5 and 7; Placebo-Withdrawal = Nights 11–12.

[b] $P < 0.05$, one-tailed (comparison of Placebo-Baseline and Treatment difference scores).

[c] $P < 0.025$, one-tailed (comparison of Placebo-Baseline and Treatment difference scores).

[d] $P < 0.005$, one-tailed (comparison of Placebo-Baseline and Treatment difference scores).

[e] $P < 0.0005$, one-tailed (comparison of Placebo-Baseline and Treatment difference scores).

In order to determine if triazolam produced "rebound insomnia" on the first withdrawal night, between-groups t-tests were performed on difference scores derived by subtracting each subject's night 11 data from his night 2 (placebo-baseline) data. No significant differences between placebo-baseline and the first withdrawal night were found on measures of sleep latency, total time awake, and total sleep time. In addition, a within-group paired t-test was performed on mean sleep latencies for the placebo-baseline and placebo-withdrawal conditions for the triazolam subjects alone. It was found that sleep latency returned to placebo-baseline values but did not exceed these values during withdrawal.

All sleep parameters which were significantly altered by triazolam during treatment returned to placebo-baseline levels during withdrawal. Consistent with the EEG data, triazolam subjects reported a significantly reduced subjective estimate of sleep latency during treatment ($t_9 = 2.4528$, $P < 0.025$).

Effects on Morning Performance and Mood. At the time of morning test sessions, approximately 8.25 hours post-administration, there were no significant differences between the placebo and triazolam groups on performance and mood measures.

Time Course of Acute Effects

Performance. Table 3 summarizes performance data for test sessions conducted during the three arousals from sleep on night 10. In addition, morning performance data obtained in testing following night 10 are presented. These morning test results are representative of all morning test sessions. For one subject in the placebo group, the second performance battery of the night was not performed, due to procedural error, thus altering the degrees of freedom reported below. Significant main effects of Groups were found for card sorting time ($F_{1,17} = 11.14$, $P < 0.004$), total correct on digit substitution ($F_{1,17} = 10.19$, $P < 0.005$), and number correct on Williams Word Memory Test (for the first list presented in each performance battery $F_{1,17} = 13.02$, $P < 0.002$ and, for the second list, $F_{1,17} = 5.81$, $P < 0.028$). Post-hoc between-groups t-tests for each test session indicated that the triazolam group performed significantly worse on each performance measure during each of the three test sessions. On the 4-Choice Reaction Time Test, data from the third nighttime test session and the morning session following night 10 on one triazolam subject were lost due to a faulty cassette tape. Because of this additional data loss, the omnibus F test was not performed for the 4-choice test but between-groups t-tests indicated that reaction time was significantly slower for triazolam subjects at each test session.

Performance data from all four tasks show a gradual recovery which begins at the time of the third test session, approximately 5 hours post-drug and, in comparison with morning performance on placebo, full recovery is seen by the time of morning testing. For example, on the Wilkinson 4-Choice Reaction Time Task, curves for the placebo group and triazolam group converge by the time of morning testing (Fig. 2). There were no significant differences between the two groups on subjective (SSS, and NHRC Mood Scale) measures.

Latency of Return to Sleep. The latency of return to sleep following nighttime testing was significantly shorter for the triazolam group for each of the three sessions (Fig. 3). The average latency of return to sleep following nighttime performance sessions was 5.10 ± 2.30 minutes for the triazolam subjects and 11.89 ± 6.87 minutes for placebo subjects ($t_{18} = 2.9641$, $P < 0.005$).

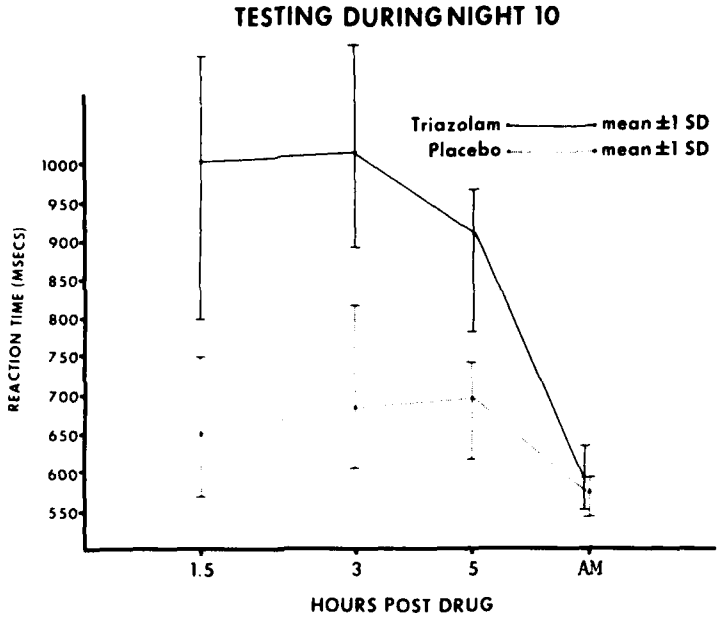

Fig. 2. Mean reaction time on the Wilkinson 4-Choice Reaction Time Task during three arousals from sleep (at 1.5, 3, and 5 hours post-drug) and for the morning test session (AM) at 8.25 hours post-ingestion.

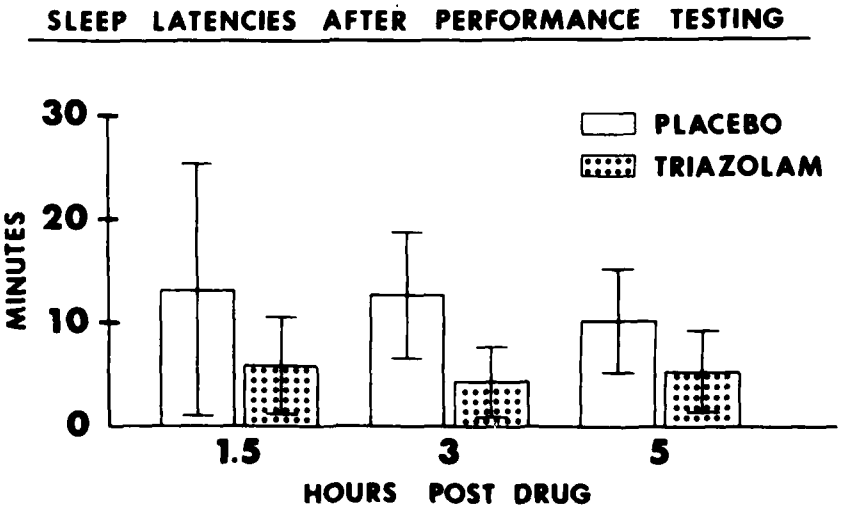

Fig. 3. Mean latencies of return to sleep following nighttime test sessions on night 10. Sleep latency is significantly shorter for the triazolam group at 1.5 hours (t_{18} = 1.7629, $P < 0.05$), at 3 hours (t_{17} = 3.7437, $P < 0.005$), and at 5 hours (t_{18} = 2.4324, $P < 0.025$).

TABLE 3

Performance During Arousals from Sleep and Morning Performance Following Night 10

Task	Hours Post-Drug	Triazolam $\bar{X}$ (± SD)	Placebo $\bar{X}$ (± SD)	t	df	$P <$
Four-Choice Reaction Time (ms)	1.5	1020. (279.)	650. (127.)	3.795[a]	17	0.005
	3	1139. (607.)	676. (101.)	2.382[a]	17	0.025
	5	908. (129.)	717. (172.)	2.599[a]	16	0.01
	8.25	598. (86.)	558. (50.)	0.0188[b]	16	n.s.
Digit Symbol Substitution (score)	1.5	32.65 (14.31)	48.89 (9.73)	2.9627[a]	18	0.005
	3	27.75 (13.44)	48.22 (7.38)	4.0460[a]	17	0.0005
	5	36.45 (15.93)	46.67 (9.22)	1.8027[a]	18	0.05
	8.25	52.70 (11.38)	59.70 (11.65)	0.1542[b]	18	n.s.
Williams Word Memory Test (No. correct)	1.5	8.70 (4.27)	13.60 (2.32)	3.1889[a]	18	0.005
	3	8.80 (3.68)	14.00 (3.46)	3.1633[a]	17	0.005
	5	11.00 (4.11)	14.40 (2.59)	2.2132[a]	18	0.025
	8.25	16.30 (3.56)	15.70 (2.45)	0.8961[b]	18	n.s.
Card Sorting Time (seconds)	1.5	171.35 (37.16)	119.28 (19.06)	3.8355[a]	18	0.005
	3	176.70 (63.92)	123.78 (22.95)	2.3458[a]	17	0.025
	5	155.15 (31.74)	120.00 (21.91)	2.7420[a]	18	0.01
	8.25	110.17 (13.22)	97.75 (9.32)	0.6607[b]	17	n.s.

[a] Results of between-groups t-tests.

[b] Results of between-groups t-tests on difference scores (mean Placebo-Baseline minus Morning score).

Effects on Memory

In the morning following night 10, triazolam subjects had a significantly lower score (number correct) on the Memory Checklist ($\bar{X}_{drug}$ = 17.30 ± 8.38 vs. $\bar{X}_{placebo}$ = 40.40 ± 18.67, t_{18} = 3.5689, $P < 0.005$). Since the target words on this checklist were words presented during the previous night on the Williams Word Memory Test, further analyses were performed to determine when memory loss had occurred. In a procedure similar to that described by Roth et al.,[22] a total night recall score for each subject was derived by summing the total number of words correctly recalled during the night on the presentations of the Williams Word Memory Test lists and then obtaining a mean percentage loss for the night. For the triazolam group, immediate loss during the night was 69.89 ± 10.07% and for the placebo group, 53.67 ± 6.75% (t_{18} = 4.2367, $P < 0.0005$). An inspection of the words correctly identified on the Memory Checklist the following morning indicated that, in addition to recognizing some words which they had correctly recalled during the night, subjects in

both groups correctly recognized target words in the morning which they had not been able to recall during nighttime testing. In order to quantify additional memory loss occurring across the night, we considered only the pool of words that the subject had correctly recalled during the night and calculated the percentage of loss from that pool--*i.e.*, the words subjects recalled correctly at night but were unable to recognize correctly on the Memory Checklist in the morning. For the triazolam group, the loss from nighttime testing to morning testing was 66.92 ± 12.11% and for the placebo group, 40.02 ± 21.92% (t_{18} = 3.3971, $P < 0.0005$).

Correlational analysis revealed a significant positive relationship between latency of return to sleep (during night 10) and Memory Checklist score in the morning. Over all subjects, the correlation coefficient, Pearson r, was 0.53 ($P < 0.025$). This relationship was significant within the triazolam group (r = 0.72, $P < 0.025$) but not within the placebo group.

Time Course of Effects on Arousal Threshold

Arousal threshold was significantly higher during treatment for triazolam subjects at the time of the first (t_{18} = 2.4370, $P < 0.025$), second (t_{16} = 5.6518, $P < 0.0005$), and third (t_{17} = 2.9334, $P < 0.005$) arousals (Fig. 4). (Not all subjects met the criteria for all arousals, thus altering the degrees of freedom reported above.) Within-groups analyses revealed that triazolam significantly raised arousal threshold for the SWS arousal (t_9 = 3.4001, $P < 0.005$); it was also found that placebo group subjects became more sensitive to the tone with repeated experience and had significantly reduced arousal threshold levels during the treatment condition for the first, second, and third arousals. Consistent with the arousal threshold data, latency of return to sleep following arousal by tones was significantly reduced for the first through third arousals in triazolam subjects during treatment.

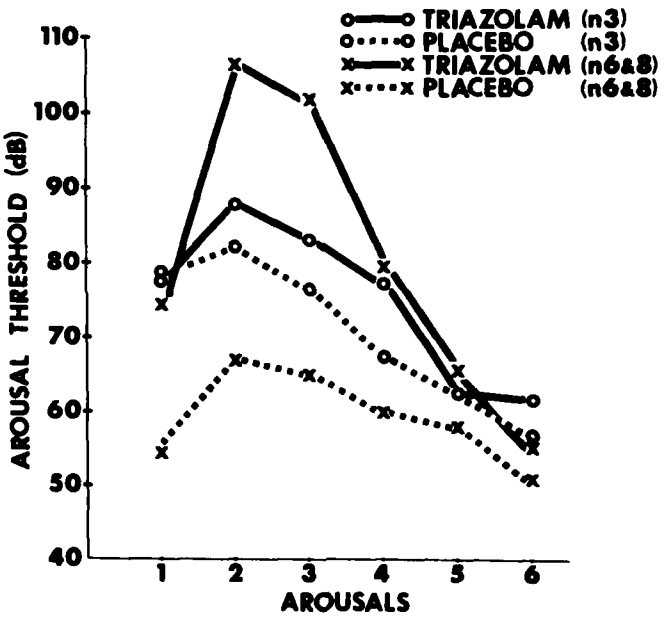

Fig. 4. Mean arousal thresholds for the placebo-baseline night (n3) and for the mean of 2 treatment nights (n6&8).

DISCUSSION

Our results replicate previous reports of the hypnotic efficacy of triazolam (0.5 mg) and further confirm the well-described effects of benzodiazepines on sleep and brain activity during sleep. Previous reports of the effects of triazolam on SWS have been inconsistent,[1,3-7,9] but, in our subjects who were screened to insure that they had adequate amounts of SWS to show an alteration, there was a highly significant reduction in Stage 4 percent. Even though the metabolic pathway of triazole benzodiazepines is different from that of flurazepam, its effects on sleep stages and spindle and delta activity are similar. The major difference between triazolam and longer-acting hypnotics in terms of sleep-related effects is that sleep measures return to baseline levels during short-term withdrawal, a finding which emphasizes, in behavioral terms, the fact that triazolam and its major metabolite, 7-α-hydroxy triazolam, are rapidly metabolized and do not appear to produce any substantial cumulative effects.

The advantages of use of a parallel, three-phase design are also emphasized by our findings. For example, in the night-by-night sleep latency data, we note the previously described but substantial effects of placebo administration in reduction of sleep latency in both groups during the placebo condition. In longer administration, placebo loses its effectiveness and sleep latencies in the placebo group become highly variable over nights. Triazolam, however, maintains the reduction in sleep latency during treatment. A finding which deserves emphasis is that our data do not show "rebound insomnia" in subjective and objective measures of sleep latency during withdrawal as has been found in previous research.[30]

The major goals of this study were (1) to determine if bedtime administration of triazolam would cause a performance decrement in the morning, and (2) to determine the behavioral time course during the night of acute effects on performance. Our results demonstrate that morning mood and performance are not deleteriously affected by administration of triazolam (0.5 mg) at bedtime. Thus, triazolam is suitable for use when the individual will not be required to perform these tasks for 8.25 hours post-administration. However, assessment of the acute effects of triazolam administration--at approximately 1.5, 3, and 5 hours post-ingestion--reveals that cognitive, memory, and visuo-motor performance are impaired. To our knowledge, this study was the first to measure the time course of drug effect during sleep on the EEG and on behavioral response through systematic arousals of the sleeping subject. Most sleep studies have looked at early morning and subsequent daytime performance. The time course of the behavioral effects following drug ingestion has also been studied in subjects who remain awake during the entire study period. It is of interest that, for triazolam, at least, the time course of drug effects on performance tasks is the same regardless of whether the subject remains awake, or is allowed to sleep and is awakened to perform. Nicholson and Stone,[7] using a 0.25 mg triazolam dose level, and a 0.4 mg brotizolam dose level,[31] reported a similar temporal change on a visual motor (tracking) task. Though the Nicholson et al. findings and ours cannot be directly compared, the similarity of results on visual motor tasks suggests that whether the subject is awake or asleep is not a major factor in the pattern of the performance change post-drug and, perhaps, in the rate of drug metabolism.

Our findings on the effects of triazolam on memory are consistent with previous reports of anterograde amnesia produced by presurgical administration of benzodiazepines[32-35] and also with

previous reports of anterograde amnesic effects of benzodiazepines administered as hypnotics.[22,36] The memory impairment associated with hypnotic use could be the result of several underlying mechanisms: a lowered arousal level during stimulus presentation, disruption of memory consolidation, or interference with retrieval mechanisms. Roth et al.[22] have recently presented data supporting the hypothesis that the mechanism of memory loss is an impairment of consolidation caused by a more rapid return to sleep following stimulus presentation on the drug nights. In our procedures, the Williams Word Memory Task was the last task presented during nighttime test sessions. Following completion of this test, the lights were turned out and subjects were instructed to return to sleep; thus, differences in wake time after completion of the task were almost entirely due to sleep latency. The significant correlation between sleep latencies during night 10 and number correct on the morning Memory Checklist indicates that rapid return to sleep may be a factor in the memory loss across the night. The time period during which memory systems are disrupted by rapid return to sleep is quite short, since, in placebo subjects who remained awake on the average about 6 minutes longer, there was no significant correlation between latency of return to sleep and morning recall.

However, the interpretation of the findings on memory are further complicated by the fact that our triazolam subjects showed a significantly larger percentage loss in immediate recall during nighttime testing on the Williams Word Memory Tests. Because of the nature of this task, in which subjects must write down each word during stimulus presentation, subjects had to attend to the stimulus material and the material received at least preliminary processing. This larger short-term loss raises the possibility that triazolam disrupts entrance of material into short-term store or reduces the number of items which can be held in short-term store for immediate retrieval. Since a wide variety of performance measures, including visuo-motor and other cognitive tasks, showed impairment during the night, a parsimonious explanation might be that arousal level is reduced due to the presence of the hypnotic in the brain. Our finding that morning recall of word pairs on the P-A task was not impaired during treatment demonstrates that triazolam administration does not produce retrograde amnesia.

Consistent with the findings describing the time course of acute effects of triazolam on performance during the night was our finding of similar effects on arousal threshold and latency of return to sleep after arousals. Our parallel design permitted us to identify the fact that with repeated exposure to the arousal tones, placebo subjects became sensitized to the tone and were aroused by tones of lower dB level. On the other hand, for triazolam subjects, the tone did not become more salient with repeated exposure and, in fact, their arousal threshold was significantly elevated above placebo values during SWS.

The focus of recent evaluations of sleep medications has been on performance effects and how long these effects persist, as well as on hypnotic efficacy. Although triazolam did not produce morning performance decrements in our study, acute effects on performance during arousals from sleep, on arousal threshold, and memory were evident. While the predictive validity of performance on laboratory tasks to real-world performance may be debated, our findings indicate that poor sleepers who take triazolam at bedtime may not respond as readily to salient signals which occur during sleep, such as smoke detectors or other alarms. Our data suggest that behaviors performed during arousals from sleep during the night, such as taking telephone calls or ingesting medications (as has been discussed by Roth et al.[22]), may be forgotten.

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(U) The effects of a short-acting benzodiazepine hypnotic, triazolam (0.5 mg), on sleep, performance, and arousal threshold were assessed in 20 male poor sleepers (age 21 ± 2.37 years). Following a laboratory screening night, all subjects received placebo for 3 nights (single-blind), 10 received triazolam and 10 placebo for 6 nights (double-blind), and all received placebo on 2 withdrawal nights (single-blind). All effects described below were statistically significant. Triazolam reduced sleep latency and increased total sleep time and sleep

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20. ABSTRACT (continued)

efficiency. Stage 2% was increased and Stage 4% was reduced during treatment. Morning performance, measured 8.25 hours post-drug, showed no decrements. Acute effects were assessed on the 6th treatment night during arousals from sleep at 1.5, 3, and 5 hours post-administration: performance was impaired in triazolam subjects on the Wilkinson 4-Choice Reaction Time Test, Digit Symbol Substitution Test, Williams Word Memory Test, and Card Sorting Task. In the morning following the 6th treatment night, long-term memory was tested using a recognition task requiring subjects to identify words presented during nighttime test batteries: triazolam subjects correctly identified fewer target words. Triazolam administration produced anterograde amnesic effects. But, in a Paired Associates Test learned prior to drug ingestion on the previous evening, triazolam did not impair morning recall of word pairs. Threshold for arousal from slow wave sleep was elevated during treatment, and triazolam subjects did not show increased sensitivity to the arousing tone over nights as did placebo subjects.